

## REMARKS

### I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons below.

### II. Status of the Claims

Claims 1-10 were cancelled previously. Claims 11-20 were presented anew, and they are now pending. Claims 11 and 16 are currently amended to specify that the compound or agent employed in the claimed methods is identified as one that causes the rate-limiting step in the biosynthetic pathway to protoporphyrin IX for heme to be bypassed. Exemplary support for the amendments can be found in the specification at paragraph 0029.

### III. The Office Action

The PTO lodged a single ground for rejection, namely that of claims 11-20 under 35 U.S.C. § 112, first paragraph for an alleged lack of enablement for precursors of protoporphyrin IX other than 5-aminolevulinic acid. Office Action at page 2. The PTO's analysis devoted commentary to each of the "Wands" factors, drawing particular attention to illustrations of the invention that employ only 5-aminolevulinic acid. *Id.* at 3-5. The PTO concluded that a skilled person would be obliged to undertake undue experimentation to identify and use other precursors of protoporphyrin IX in the claimed invention. To the extent that the rejection might apply to the claims as amended, Applicants respectfully traverse.

The claims as amended are enabled because the administered compound or agent as defined in the claims is well-known in the art. "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." MPEP § 2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert denied*, 480

U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In this case, the scope of compounds or agents useful in the invention was known to the skilled artisan, because they would have understood what compounds would allow the bypassing of the rate-limiting step in the heme biosynthetic pathway and inducing synthesis of protoporphyrin IX. Additionally, the skilled artisan has at his disposal time-honored and well known synthetic methodology by which to apprehend compounds and agents that will provide such compounds. Making such substances, therefore, are well within the purview of the skilled artisan.

To illustrate the heme biosynthetic pathway, Applicants kindly refer the PTO to McGilvery et al., Biochemistry: A Fundamental Approach 632-635 (2d ed. 1979) (Exhibit 1). Showing the heme biosynthetic pathway, the excerpt illustrates the role of 5-aminolevulinate. Compounds useful in the invention include those compounds that are implicated in the biosynthetic pathway of heme as shown in McGilvery et al.

Additionally, the present specification teaches at paragraph 0029 that “the usual rate-limiting step in the [heme biosynthetic] process, the synthesis of 5-aminolevulinic acid, can be bypassed by the provision of exogenous ALA, porphobilinogen or other precursor of PpIX.” The skilled artisan would understand an “other precursor” of protoporphyrin IX to include *prodrugs* of compounds in the heme biosynthetic pathway. Such prodrugs, by definition, provide the desired compound after administration. Illustrative of an “other precursor” in this context is an ester of 5-aminolevulinic acid. Also, Applicants submit De Matties et al., “Brain 5-aminolaevulinate synthase,” Biochemical Journal, vol. 196, 811-817 (1981) (Exhibit 2). De Matties et al. disclose that “the methyl ester [of 5-aminolevulinic acid] reflects passive diffusion of the unchanged methyl ester across the blood/brain barrier, followed by hydrolysis to the free amino acid within the brain and subsequent conversion of 5-aminolaevulinate into haem.” The passage thus reflects knowledge at the time of the invention that an agent such as an ester of 5-aminolevulinic acid could be administered to a patient to achieve conversion into heme and, accordingly, achieve the synthesis of protoporphyrin IX (a precursor to heme).

Also, Applicants submit Srivastava et al., "Regulation of 5-Aminolevulinate Synthase mRNA in Different Rat Tissue, " Journal of Biological Chemistry, vol. 263, 5202-5209 (1988) (Exhibit 3) to further support the knowledge at the time of the invention that an ester of 5-aminolevulinic acid, such as the methyl ester, was known to enter the heme biosynthetic pathway via 5-aminolevulinic acid and therefore is active in inducing synthesis of protoporphyrin IX (a precursor to heme). Srivastava et al. disclose that "[a]dministration of hemin to rats reduced the basal level of this mRNA [a specific 5-aminolevulinate synthase] only in liver, but the heme precursor, 5-aminolevulinate (or its methyl ester) repressed the basal levels in liver, kidney, heart, testis and brain."

Because the skilled artisan would have known already what compounds would be available and effective as such precursors, he would not have had to "envision formulation, dosage, duration, route, and . . . an appropriate animal model system for the claimed compound." Office Action at page 4. Thus, while *some* experimentation might have been incumbent upon the artisan, and therefore entirely consistent with the standard under section 112, it certainly would not have been *undue* experimentation, as the universe of possible compounds prescribed by the claims was much smaller than what the PTO attached to the endeavor allegedly besetting the skilled artisan.

Therefore, at the time of the invention, the skilled artisan would have indeed appreciated what compounds are contemplated by the claims: substances such as 5-aminolevulinic acid as described in the present specification, the shown and listed precursors of PpIX as described by McGilvery in Biochemistry and esters of 5-aminolevulinic acid, such as the methyl ester of 5-aminolevulinic acid as described by Srivastava et al. and De Matties et al. Accordingly, the claims are enabled. Applicants therefore courteously request the PTO to reconsider and withdraw this ground for rejection

#### IV. Conclusion

Now having addressed the only ground for rejection, Applicants believe that the present application is in condition for allowance. Accordingly, they request favorable

reconsideration of the application as amended. The Examiner is invited to contact the undersigned by telephone if the Examiner feels that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date March 13, 2007

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.